

REMARKS

Claim Amendments

Claims 1-2, 15-17, 24, 27, and 31-37 are pending. Claims 31-37 are added. Support for the new claims can be found throughout the specification and in the claims as originally filed. *See, e.g.*, Example 2B.² Applicants respectfully request entry of the above amendment and submit that the above amendment does not constitute new matter.

Withdrawn Objections and Rejections

Applicants appreciate the Examiner's withdrawal of the objections and rejections under 35 U.S.C. § 112.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-6, 10-18, 20-21, 24, 27, and 30 stand rejected under 35 U.S.C. § 103 as being obvious over U.S. Pat. No. 7,135,621 ("Yanofsky") in view of Smith, *et al.* (Nature 407: 319-320, 2000) ("Smith").

Applicants respectfully traverse.

I. The USPTO Fails To Establish A *Prima Facie* Case Of Obviousness

The USPTO contends that one of ordinary skill in the art would have been motivated to combine Yanofsky and Smith.

Applicants' previous response argued that one of ordinary skill in the art would not be motivated to modify Yanofsky's method to obtain a *milder* silencing of the IND genes by replacing Yanofsky's antisense fragment with Smith's hairpin dsRNA structure—a structure that *enhances* silencing.³

Applicants maintain that the USPTO has not established a *prima facie* case of obviousness. Indeed, the USPTO fails to articulate why one of skill in the art would add a construct that enhances gene silencing to achieve a method that weakens gene silencing. On the contrary, it seems clear that one of ordinary skill in art would not use a construct that accomplishes the opposite effect of the method. Accordingly, Applicants submit that not only is there is no reason to combine Yanofsky and Smith, one of ordinary skill in the art would be discouraged from combining these references.

² All paragraph numbers cited herein refer to the paragraph numbers set forth in U.S. 2006/0248612, the publication of the instant application.

³ *See* Applicants' response, filed March 7, 2008, pages 11-12.

II. The Specification And Dr. Botterman's Declaration Demonstrate Unexpected Results

The USPTO fails to establish a *prima facie* case of obviousness. As such, a submission of unexpected results is not required. Applicants, however, provide such evidence.

A. The Specification Demonstrates Unexpected Results.

Applicants submit that the specification discloses unexpected results. In particular, the specification states:

The invention is based on the unexpected observation that moderate dsRNA gene silencing of genes involved in the development of the dehiscence zone and valve margins of pods in *Brassicaceae* plants, particularly oilseed rape plants, allows the isolation of transgenic lines with increased pod shatter resistance and reduced seed shattering, the pods of which however may still be opened along the dehiscence zone by applying limited physical forces. This contrasts with transgenic *Brassicaceae* plants, wherein the dsRNA silencing is more pronounced, such as the ones described in the art, which result in transgenic lines with indehiscent pods, which no longer can be opened along the dehiscence zone, and which only open after applying significant physical forces by random breakage of the pods, whereby the seeds remain predominantly within the remains of the pods.⁴

This statement is supported by Example 2B. In Example 2B, a chimeric gene comprising a at least 200 consecutive nucleotides of the nucleotide sequence of SEQ ID NO: 1 other than a bHLH encoding region was introduced into *B. napus*. These transformed plants had improved pod shatter resistance with agronomically relevant threshability. Accordingly, the specification provides evidence demonstrating the unexpected results of the claimed invention.

B. Dr. Botterman's Declaration Demonstrates Unexpected Results.

Applicants also submit herewith a declaration under 37 C.F.R. § 1.132 of Dr. Johan Botterman.

Dr. Botterman has been associated with the field of plant biology and biotechnology for more than 20 years.⁵ Dr. Botterman is a person of at least ordinary skill in the art and was such a person prior to June 23, 2003, the foreign priority date claimed in the above-identified application.⁶

⁴ Specification, ¶ 48; *see also* Example 2B.

⁵ Declaration under 37 C.F.R. § 1.132 of Dr. Johan Botterman ("Botterman Dec."), ¶¶ 2-3.

⁶ *Id.* at ¶ 4.

1. The Cited References

Yanofsky (and Liljegren) disclose the identification of the INDEHISCENT1 (IND1) gene from *Arabidopsis thaliana*, the identification and analysis of *Arabidopsis* plants containing a mutation in the IND1 gene which results in indehiscent fruits, as well as promoter/enhancer::GUS fusions of the IND1 gene.⁷ When the IND1::GUS fusions were introduced in *Arabidopsis* wild-type plants, about 25% of the transgenic lines failed to express significant GUS activity and displayed an indehiscent phenotype.⁸ The references suggest that the most likely explanation of these results is that the IND1::GUS fusions, as well as the endogenous IND1 gene were co-suppressed.⁹

The Yanofsky application is a continuation-in-part of the Liljegren application. Yanofsky discloses the nucleotide sequence of two IND1 orthologs from *Brassica napus*.¹⁰ This information was added to Yanofsky at a later date than the foreign priority date claimed in the instant application. Accordingly, Yanofsky's disclosure of the two IND1 orthologs from *Brassica napus* is not prior art to the instant application.

The Examiner asserts that Smith teaches (1) a DNA construct that produces hairpin loop type of dsRNA (hpRNA) with functional (i.e. splicable) intron as spacer enhances silencing efficiency; and (2) the modifications that help to align the complementary arms of the hairpin and promote the formation of a duplex could increase the efficiency of gene silencing.

Dr. Botterman agrees with the Examiner's characterization of Smith.¹¹ Dr. Botterman, however, disagrees with the Examiner's contention that one of ordinary skill in the art would be motivated (or have a reason) to modify Yanofsky's (or Liljegren's) method to achieve the claimed methods by replacing Yanofsky's (or Liljegren's) antisense fragment with Smith's hairpin structure.¹² The claimed invention concerns the *weakening* of gene silencing of the IND1 gene, whereas Smith concerns *enhancing* gene silencing in general.¹³ Therefore, in Dr.

⁷ *Id.* at ¶ 9.

⁸ *Id.*

⁹ *Id.*

¹⁰ *Id.* at ¶ 10; *see also* Yanofsky, paragraph bridging col. 6-7, Figures 1 and 2, Example 2.

¹¹ Botterman Dec., ¶ 11.

¹² *Id.*

Botterman's opinion, one of ordinary skill in the art would actually be discouraged from combining Yanofsky (or Liljegren) and Smith to achieve the claimed methods.

2. Knowledge Of The Skilled Artisan

Prior to June 23, 2003, the foreign priority date claimed in the instant application, the nucleotide sequences of IND1 orthologs from *Brassica* plants were not publicly known.¹⁴ Accordingly, a person skilled in the art could not have made any prediction of the degree of sequence identity between the *Arabidopsis* IND1 gene and the orthologs from *Brassica napus* plants or any subparts thereof such as the bHLH domain coding region.¹⁵

Prior to June 23, 2004, the filing date of the '793 application, a person of ordinary skill in the art would have been aware of the (probable) co-suppression results reported in and Yanofsky and Liljegren (discussed above), which resulted in indehiscent phenotypes.¹⁶ The skilled artisan would also have known that silencing of the IND gene in *Arabidopsis thaliana* using so-called dsRNA silencing techniques resulted in almost complete podshatter resistance, and that 98% of the transgenic *Arabidopsis* lines developed siliques, which did not open along the valve suture and could only be opened by applying considerable pressure to the valves.¹⁷

As discussed above, one of ordinary skill in the art would not have combined Yanofsky (or Liljegren) with Smith. Even assuming that one of ordinary skill in the art would have combined the teaching of Yanofsky (or Liljegren) with the teaching of Smith and (1) constructed a chimeric gene encoding a dsRNA based on part of the *Arabidopsis* IND1 nucleotide sequence; and (2) introduced the chimeric gene into an oilseed rape plant, then the skilled person would, in Dr. Botterman's opinion, only expect two possible outcomes:

(a) the nucleotide sequences of the dsRNA based on *Arabidopsis* IND1 and of the endogenous IND1 *Brassica* orthologs are sufficiently identical to allow gene-silencing to be established and consequently an indehiscent phenotype as observed in *Arabidopsis* would be expected (see discussion above); or

¹³ *Id.*

¹⁴ *Id.* at ¶ 12. As discussed above, Yanofsky's disclosure of IND1 orthologs from *Brassica napus* were disclosed after the foreign priority date claimed in the instant application.

¹⁵ *Id.*

¹⁶ *Id.* at ¶ 13.

¹⁷ *Id.*

(b) the nucleotide sequences of the dsRNA based on *Arabidopsis* IND1 and of the endogenous IND1 *Brassica* orthologs are too divergent for any gene-silencing phenomenon to be established and no effect on *Brassica* IND1 gene expression and dehiscence phenotype are to be expected.¹⁸ In view of the knowledge of one of ordinary skill in the art, at the time the instant application was filed, Dr. Botterman's opines that a person of ordinary skill in the art would probably have favored option (a).¹⁹

It is also Dr. Botterman's opinion that a person of ordinary skill in the art would not have been in a position to predict that the use of dsRNA based on parts of the nucleotide sequence of IND1 from *Arabidopsis* would result in *Brassica* plants with an intermediate degree of gene-silencing sufficient to prevent seed shattering, but not so extensive as to prevent the normal opening along the dehiscence zone with the application of moderate physical forces common in agricultural practices such as the use of combine harvesters.²⁰

Dr. Botterman concludes that it was unexpected that a chimeric gene encoding a dsRNA based on part of the nucleotide sequence of the *Arabidopsis* IND1 gene not including a bHLH domain coding region would result in an increased pod shatter resistance combined with an agronomically relevant threshability of the pods in *Brassica* species such as *B. napus*, *Brassica juncea*, and *Brassica campestris*.²¹

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

Claims 1-6, 10-18, 20-21, 24, 27, and 30 stand rejected under 35 U.S.C. § 103 as being obvious over U.S. Patent No. 6,998,517 ("Liljegren") in view of Smith.

Applicants respectfully traverse and request withdrawal of this rejection for the same reasons discussed above.

¹⁸ *Id.* at ¶ 14.

¹⁹ *Id.* at ¶ 15.

²⁰ *Id.* at ¶ 16.

²¹ *Id.* at ¶ 17.

Nonstatutory Obviousness-Type Double Patenting

Claims 1-6, 10-18, 20-21, 24, 27, and 30 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-39 Liljegren in view of Smith.

Applicants respectfully traverse and request withdrawal of this rejection for the same reasons discussed above.

Claims 1-6, 10-18, 20-21, 24, 27, and 30 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-28 of Yanofsky in view of Smith.

Applicants respectfully traverse and request withdrawal of this rejection for the same reasons discussed above.

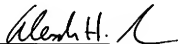
CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this Response, the Examiner is invited to contact the Applicant's undersigned representative to discuss and resolve such issues.

Respectfully submitted,

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